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Response of White Leghorn Chickens of Various Genetic Lines to Infection with Avian Leukosis Virus Subgroup J

Susan M. Williams,[ABC] Willie M. Reed,[B] Larry D. Bacon,[A] and Aly M. Fadly[AD]

[A]U.S. Department of Agriculture, Agricultural Research Service,
Avian Disease and Oncology Laboratory, 3606 East Mount Hope Road,
East Lansing, MI 48823
[B]Department of Pathobiology and Diagnostic Investigation, A522 East Fee Hall,
Michigan State University, East Lansing, MI 48824

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SUMMARY. In Experiment 1, chickens from various white leghorn experimental lines were inoculated with strain ADOL-Hcl of subgroup J avian leukosis virus (ALV-J) either as embryos or at 1 day of age. At various ages, chickens were tested for ALV-J induced viremia, antibody, and packed cell volume (PCV). Also, at 4 and 10 wk of age, bursal tissues were examined for avian leukosis virus (ALV)-induced preneoplastic lesions with the methyl green–pyronine (MGP) stain. In Experiment 2, chickens harboring or lacking endogenous virus 21 (EV21) were inoculated with strain ADOL-Hcl of ALV-J at hatch. All embryo-inoculated chickens in Experiment 1 tested positive for ALV-J and lacked antibody throughout the experimental period of 30 wk and were considered viremic tolerant, regardless of line of chickens. By 10 wk of age, the incidence of ALV-J viremia in chickens inoculated with virus at hatch varied from 0 (line 0 chickens) to 97% (line $15I_5$); no influence of ALV-J infection was noted on PCV. Results from microscopic examination of MGP-stained bursal tissues indicate that ALV-J can induce typical ALV-induced transformation in bursal follicles of white leghorn chickens. Lymphoid leukosis and hemangiomas were the most common ALV-J–induced tumors noted in chickens in Experiment 1. At termination of Experiment 2 (31 wk of age), 54% of chickens harboring EV21 were viremic tolerant compared with 5% of chickens lacking EV21 after inoculation with ALV-J at hatch. The data indicate that genetic differences among lines of white leghorn chickens, including the presence or absence of EV21, can influence response of chickens to infection with ALV-J.

RESUMEN. Respuesta de aves tipo leghorn de varias líneas genéticas a la infección por virus de la leucosis aviar del subgrupo J.

En un primer experimento se inocularon embriones y aves de un día de edad de varias líneas experimentales de aves tipo leghorn con la cepa ADOL-Hcl del virus de la leucosis aviar del subtipo J (ALV-J). Se examinaron las aves a varias edades para determinar la presencia de viremia y anticuerpos y para determinar los valores del hematocrito. También se tomaron muestras de bolsas de Fabricio a las 4 y 10 semanas de edad para determinar la presencia de lesiones preneoplásicas mediante la técnica de tinción de verde metil pironina (MGP por sus siglas en inglés). En un segundo experimento se inocularon al momento del nacimiento aves positivas y negativas a la presencia de virus de leucosis endógeno tipo 21 (EV21) con la cepa ADOL-Hcl del virus J. Todas las aves inoculadas en la etapa embrionaria y al nacimiento en el primer experimento fueron positivas a la presencia del virus y no presentaron anticuerpos durante la duración del experimento (30 semanas), por lo cual se consideró que las aves eran virémicas y tolerantes, sin importar el linaje genético de donde procedían. La incidencia de viremia a las 10 semanas de edad en las aves inoculadas al día de edad varió de un 0% (línea 0) a un 97% (línea $15I_5$), sin que se encontrara ninguna influencia del virus sobre el hematocrito de las aves.

[C]Present address: Department of Avian Medicine, College of Veterinary Medicine, University of Georgia, Athens, GA 30602.
[D]Corresponding author.

El examen microscópico de las muestras de bolsa de Fabricio teñidas con MGP indicó que el virus de leucosis J puede inducir transformaciones de los folículos del órgano en aves tipo Leghorn. Los tipos de tumores más frecuentes observados en las aves inoculadas con el virus de leucosis J del experimento 1 fueron la leucosis linfoide y hemangioma. Al final del experimento 2 (31 semanas de edad), 54% de las aves positivas a la presencia del virus EV21 mostraron estar virémicas y tolerantes en comparación con el 5% de las aves negativas a la presencia del EV21, luego de la inoculación con el virus de leucosis J al momento del nacimiento. Estos datos sugieren que la presencia o ausencia del EV21 puede influenciar la respuesta de las aves a la infección por el virus de leucosis J.

Key words: avian leukosis virus subgroup J, white leghorn chickens, endogenous virus 21, lymphoid leukosis

Abbreviations: Ab = antibody; ADOL = Avian Disease and Oncology Laboratory; ALV = avian leukosis virus; ALV-A, ALV-B, ALV-J = avian leukosis virus subgroups A, B, J; CEF = chicken embryo fibroblast; *ev* = endogenous virus gene; EV21 = endogenous virus 21; HEM = hemangioma; IU = infectious units; LL = lymphoid leukosis; MGP = methyl green–pyronine; ML = myeloid leukosis; PCV = packed cell volume; RAV-0, RAV-1 = Rous-associated virus, types 0, 1; RT = renal tumors; *tv*A, *tv*B = tumor virus subgroups A, B receptor; VI = virus isolation

Avian leukosis virus (ALV), a retrovirus, is widespread in chickens, although the incidence of clinical disease is low (9,22). Whereas ALV induces a variety of neoplasms at various incidences, lymphoid leukosis (LL), a B-cell lymphoma, is the most common (9,22). ALV subgroup J (ALV-J), an ALV associated with myeloid leukosis (ML) in meat-type chickens, was first reported in 1991 in England (21,23,24) and has now been reported in many other countries (1,16,20).

The presence of endogenous viral (*ev*) genes within the chicken genome causes chickens to be more susceptible to infection with exogenous ALV (11,13,15,30,32). One important *ev* gene, *ev*21, encodes a complete endogenous virus named EV21 (10). The *ev*21 locus has been reported to be closely associated with the sex-linked slow-feathering (late-feathering) gene, *K* (4). Most chicken breeders have integrated the late-feathering gene into the maternal parent line in order to reduce costs associated with vent sexing (4). However, decreased egg production that occurs in progeny from late-feathering dams has been associated with an increase in the incidence of infection with exogenous ALVs (19).

ALV-J infection in egg-type chickens has caused a variety of tumors that develop at a lower incidence than those seen in meat-type chickens (24). Most recently, a recombinant ALV with subgroup B envelope and subgroup J long terminal repeat has been associated with a natural outbreak of ML in commercial layers (18). The purpose of this study was to examine the response of various lines of white leghorn chickens to infection with strain ADOL-Hcl of ALV-J (16).

MATERIALS AND METHODS

Chickens. Day-old chicks or 7-day-old embryos from six lines of white leghorn chickens maintained at the USDA, Avian Disease and Oncology Laboratory (ADOL), East Lansing, MI, were used (3). The breeder flocks are free of many avian pathogens, including ALV, as determined by routine serologic surveys. Birds were housed by line and treatment and kept in plastic isolators with positive-filtered airflow and given food and water *ad libitum.*

Virus. Strain ADOL-Hcl of ALV-J (16) was used. The virus was propagated and titrated on chicken embryo fibroblasts (CEFs) obtained from line 0 chickens, a C/E (resistant to infection with endogenous ALV) line that also lacks *ev* genes (12). Chicks or embryos were each inoculated intra-abdominally (i.a.) or via the yolk sac, respectively, with 10^4 infectious units (IU).

Virologic and serologic assays. Plasma from all chickens was tested for the presence of ALV as described (17). Briefly, plasma samples were inoculated on C/E line 0 CEFs; 7–9 days later, cell lysates were tested for the presence of ALV group-specific antigen (p27) by an enzyme-linked immunosorbent assay (31). Samples were tested for ALV-J antibody by a micro-neutralization test (17).

Hematologic assay. Packed cell volumes (PCVs) were performed with whole blood samples in micro-hematocrit tubes (Oxford Labware; Sigma, St. Louis, MO) filled to appropriate levels and spun for 3 min. Each tube was hand read with the use of the Lancer Critocap Microhematocrit Capillary Tube Reader card.

Methyl green–pyronine (MGP) assays. Early transformation of bursal follicles was determined by microscopic examination of bursal tissue stained with MGP. Bursal tissues were collected and plica separated

Table 1. Viremia and antibody in chickens of various white leghorn lines inoculated as embryos or at hatch with strain ADOL Hc-l of ALV-J.

Age at inoculation	Line	Age at testing[A] 4 wk VI[B]	4 wk Ab[C]	10 wk VI	10 wk Ab	30 wk VI	30 wk Ab
Embryo	Line 0	40/40 (100)[a]	0/40 (0)[a]	26/26 (100)[a]	0/26 (0)[a]	7/7 (100)[a]	0/7 (0)[a]
1 day of age		13/44 (30)[b]	12/44 (27)[b]	0/37 (0)[b]	28/37 (76)[b]	0/28 (0)[b]	26/28 (93)[b]
Embryo	$15I_5$	40/40 (100)[a]	0/40 (0)[a]	34/34 (100)[a]	0/34 (0)[a]	17/17 (100)[a]	0/17 (0)[a]
1 day of age		44/44 (100)[a]	0/44 (0)[a]	36/37 (97)[a]	13/37 (35)[b]	30/30 (100)[a]	13/30 (43)[b]
Embryo	6_3	21/21 (100)[a]	0/21 (0)[a]	15/15 (100)[a]	0/34 (0)[a]	8/8 (100)[a]	0/8 (0)[a]
1 day of age		16/16 (100)[a]	1/16 (6)[a]	11/12 (92)[a]	1/12 (8)[a]	4/5 (80)[a]	1/5 (20)[a]
Embryo	7_1[D]	3/3 (100)	0/3 (0)	2/2 (100)	0/2 (0)	1/1 (100)	0/1 (0)
1 day of age		18/18 (100)	3/18 (17)	3/14 (21)	13/14 (93)	5/6 (83)	6/6 (100)

[A]Values are number positive/number tested (% in parentheses). Values within a genetic line of chicken with different lowercase superscripts at ages indicated are statistically different (embryo *vs* 1 day of age) with a *p*-value of ≤ 0.05 for that assay, as tested by chi-square analysis.

[B]VI = virus isolation. All embryo-inoculated chickens tested positive for ALV-J at hatch (data not shown).

[C]Ab = antibody detected to ALV-J.

[D]Entries on line 7_1 were not tested because of small numbers.

and placed flat in cassettes, usually two to three cassettes per bird. Tissues were embedded in paraffin, sectioned, and stained with MGP stain (8,27). Eight to 12 sections of bursal tissue per chicken were examined. Bursal tissue was considered positive if one follicle had evidence of transformation (appeared pyroniphilic or more eosinophilic) after examination of all bursal sections for that bird. Tissues from chickens infected as embryos or at hatch with Rous-associated virus, type 1 (RAV-1), a subgroup A ALV (ALV-A), were used as positive controls.

Pathology. All chickens that died during the experimental period (Experiment 1, 30 wk; Experiment 2, 31 wk) and those that were euthanatized at the end of each experiment were examined for gross and microscopic lesions of ALV-J–induced tumors as described (24).

Experimental design. *Experiment 1.* Chickens from four ADOL lines (0, $15I_5$, 6_3, and 7_1) were separated into three groups. Chickens in group 1 were inoculated as 7-day-old embryos via the yolk sac (75 embryos/line) with 10^4 IU of ALV-J. Chickens in group 2 (50 chicks/line) were inoculated i.a. at hatch with 10^4 IU of ALV-J. Chickens in group 3 (20 chicks/line) served as uninoculated controls. At hatch (only embryo-inoculated chickens), 4, 10, and 30 wk of age, chickens were tested for ALV-J and antibody. At 4, 10, 20, and 30 wk of age, blood from chickens in various treatment groups was analyzed for PCV. At 4 and 10 wk of age, bursal tissues from five chickens randomly selected from each treatment group, including the positive control group (inoculated with RAV-1), were examined for bursal transformation. Bursal transformation was determined by microscopic examination of tissues stained with MGP as indicated above.

Experiment 2. Progeny chickens from a cross between males of ADOL line 0.44-EV21+ (late feathering) and females of the early-feathering line $15B_1$ were used (3). The F_1 progeny of this cross are either late-feathering chicks (both male and female) that are EV21+ or early-feathering chicks (both male and female) that are EV21−. At hatch, chicks were separated into early- or late-feathering groups according to feather phenotype (28,29,30). Also, at hatch, each chicken was inoculated i.a. with 10^4 IU of ALV-J. At 4, 10, 18, and 31 wk of age, chickens were tested for ALV-J and antibody. To confirm feather phenotype, blood was also assayed for endogenous virus by a hemagglutination assay with R2 antibody at 10 wk of age (2,5).

Statistical analysis. Statistical analysis was performed with the SAS 8.0 program. Data on viremia and antibody were analyzed by a chi-square test. Results were considered significant at a level of $P \leq 0.05$.

RESULTS

Viremia and antibody. Table 1 shows results from virologic and serologic assays conducted in Experiment 1. The embryo-inoculated groups tested positive for virus at hatch and were viremic tolerant (persistent viremia and lack of antibody), regardless of line of chicken. The negative control groups for each line were negative for virus and antibodies throughout the experiment (data not shown). Because of a management accident during the first week of life, only three embryo-inoculated chickens

Table 2. Bursal transformation in chickens of various white leghorn lines inoculated as embryos or at hatch with ALV.[A]

Line of chicken	Virus	Age at testing[B]			
		Embryo		Day of hatch	
		4 wk	10 wk	4 wk	10 wk
0	ALV-J	1/5	0/5	1/5	0/4
$15I_5$	ALV-J	0/5	0/5	0/5	2/5
6_3	ALV-J	0/5	1/5	0/4	0/5
7_1	ALV-J	0/1	0/1	0/5	1/5
$15I_5 \times 7_1$	ALV-A	3/5	5/5	3/5	5/5

[A]Determined by microscopic examination of MGP-stained bursal tissue. A chicken was considered positive if one bursal follicle had evidence of transformation (appeared pyroniphilic or more eosinophilic) after examination of 8–12 sections of bursal tissue per chicken.

[B]Number positive/number tested.

in line 7_1 survived to 4 wk of age. By 4 wk of age, 27% of line 0 chickens inoculated with ALV-J at hatch developed antibody compared with 17%, 6%, and 0 in line 7_1, line 6_3, and line $15I_5$, respectively. By 10 wk of age, there was no evidence of viremia in line 0 chickens inoculated with ALV-J at hatch. In contrast, 97%–100% of line $15I_5$ chickens were viremic at 10 and 30 wk of age, respectively; however, 13 of 30 (43%) of these chickens tested positive for ALV-J neutralizing antibody at 30 wk of age. Chickens of lines 6_3 and 7_1 inoculated with ALV-J at hatch also had various degrees of neutralizing antibody but could not completely neutralize circulating virus as demonstrated by the presence of virus at 30 wk. Also, the PCV values in infected chickens were comparable with those in uninfected controls, regardless of line of chickens (data not shown).

Transformation of bursal follicles. In MGP-stained bursal sections, transformed bursal follicles appeared pyroniphilic (more eosinophilic) compared with nontransformed surrounding follicles. Also, transformed follicles exhibited disrupted architecture, namely, the cortex and medulla were indistinguishable. The incidence of transformation of bursal follicles in chickens inoculated with ALV as embryos or at hatch is presented in Table 2. At 4 and 10 wk of age, transformed bursal follicles were detected in 0–20% and 0–40%, respectively, of chickens inoculated with ALV-J. Whereas 60% and 100% of $15I_5 \times 7_1$ chickens inoculated with ALV-A (positive controls) had evidence of transformed bursal follicles at 4 and 10 wk of age, respectively. Uninoculated controls from all lines had no evidence of bursal transformation.

ALV-induced tumors. The incidence and type of ALV-J-induced tumors are shown in Table 3. The highest incidence of tumors was noted in chickens of lines 0, $15I_5$, and 7_1 (only one chicken was at risk and developed tumors). The incidence of tumors in chickens of lines, 0, $15I_5$, and 6_3 inoculated with ALV-J as embryos varied from 20% to 73% compared with 0–33% in chickens inoculated at hatch. Among chickens inoculated with ALV-J as embryos, the incidence of tumors in line 0 chickens was significantly higher ($P \leq 0.01$) than that in line

Table 3. ALV-J–induced tumors in chickens of various lines of white leghorn inoculated as embryos or at hatch with strain ADOL-Hcl of ALV-J.[A]

Age at inoculation	Line	LL	ML	HEM	RT	Other	Chickens with tumor/no. at risk[B] (%)
Embryo	0	7	1	1	2	1	11/15 (73)
1 day of age		2	0	4	0	1	7/29 (24)
Embryo	$15I_5$	0	0	4	1	2	7/17 (41)
1 day of age		4	0	3	0	1	6/31 (19)
Embryo	6_3	1	0	0	0	0	1/5 (20)
1 day of age		0	0	0	0	0	0/5 (0)
Embryo	7_1	0	0	1	0	0	1/1 (100)
1 day of age		0	0	1	1	0	2/6 (33)

[A]LL = lymphoid leukosis; ML = myeloid leukosis; HEM = hemangioma; RT = renal tumors; other = chondrosarcoma, erythroblastosis, fibromas.

[B]No. at risk = number of chickens that died with tumors plus number of chickens that survived to end of experiment. Comparison of ALV-J–induced tumors between lines (excluding line 7_1) revealed that only percentage of total tumors in chickens of line 0 inoculated as embryos with ALV-J was significantly different ($P \leq 0.01$) from that in chickens of line 6_3.

Table 4. ALV-J–induced viremia and antibody in white leghorn chickens harboring or lacking EV21.

	Age at testing (% Positive)[A]							
	4 wk		10 wk		18 wk		31 wk	
EV21	VI[B]	Ab[C]	VI	Ab	VI	Ab	VI	Ab
+	93[a]	0[a]	93[a]	16[a]	54[a]	51[a]	60[a]	43[a]
−	43[b]	0[b]	23[b]	83[b]	5[b]	98[b]	13[b]	74[b]

[A]Within a column, percentages followed by different lowercase superscripts differ significantly ($P < 0.05$). At each interval, 35–40 chickens from each group were tested for ALV-J viremia and antibody.

[B]VI = virus isolation performed on line 0 (C/E) CEF.

[C]Ab = antibody presence to ALV-J as determined by virus neutralization assays.

6_3. Also, statistical analysis of data obtained from chickens inoculated with ALV-J at hatch (excluding line 7_1) indicated no significant difference in tumor response among various lines of chickens. Some chickens had more than one tumor type when examined. Uninoculated negative control chickens had no evidence of tumors.

Influence of EV21 on ALV-J infection and tumors (Experiment 2). Table 4 shows the incidence of ALV-J induced viremia and antibody in chickens harboring or lacking EV21. At 4 wk of age, 93% of the chickens harboring EV21 were viremic compared with only 43% of chickens lacking EV21. By 10 wk of age, 16% of chickens harboring EV21 had detectable levels of antibody compared with 83% of chickens lacking EV21. At 18 wk of age, 54% of chickens harboring EV21 had detectable antibody compared with 98% of chickens lacking EV21. Table 5 shows the incidence of viremic tolerance (V+, A–) in chickens harboring or lacking EV21. By 31 wk of age, 54% of chickens harboring EV21 were classified as V+, A– compared with 5% of the chickens lacking EV21. The incidence of tumors in chickens harboring EV21 (5/31; 13.8%) was significantly higher ($P \leq 0.01$) than that in chickens lacking EV21 (1/37; 2.6%).

DISCUSSION

Chicks congenitally infected with ALV remain viremic tolerant throughout their lives (22). Data presented in this study demonstrate that embryonic inoculation of ALV-J resulted in tolerant infection, regardless of line of chicken used. Line 0 chickens (lacking *ev* genes) inoculated with ALV-J at hatch had the lowest incidence of viremia at 4 wk of age and were first to develop antibody, suggesting that lack of endogenous viral genes may influence the response of chickens to ALV-J. Previous experiments studying ALV-A (RAV-1) infection in different genetic lines of chickens harboring various *ev* genes demonstrated the development of antibodies at a slower pace than in line 0 chickens, which lack *ev* genes (10,12). The *ev* genes in chickens render chickens more susceptible to infection with other exogenous ALVs (12). This finding was also confirmed in Experiment 2 because the highest incidence of ALV-J viremic-tolerant chickens was noted in the group harboring EV21. The effects of EV21 on ALV-A–induced viremia, cloacal shedding, and neutralizing antibodies in chickens congenitally infected with EV21 have been reported (28). RAV-0, another strain of endogenous ALV encoded at the *ev*2 locus along with the *ev*3 locus has also induced immunologic tolerance in chickens infected with subgroups A and B ALV (11,13). Data from the present study clearly show that the presence of EV21 increases the susceptibility of white leghorn chickens tested to infection with strain ADOL-Hcl of ALV-J.

Table 5. Incidence of ALV-J–induced immunologic tolerance (viremia positive, antibody negative) in white leghorn chickens harboring or lacking EV21.

	Age at testing (%)[A]			
EV21	4 wk	10 wk	18 wk	31 wk
+	93[a]	66[a]	49[a]	54[a]
−	43[b]	5[b]	3[b]	5[b]

[A]Within a column, percentages followed by different lowercase superscripts letter differ significantly ($P < 0.05$). At each interval, 35–40 chickens from each group were tested for ALV-J viremia and antibody.

The loci *tv*A and *tv*B (tumor virus subgroups A and B receptors) encode receptors that are important in determining the host cellular resistance or susceptibly to ALV-A and ALV-B infection, respectively (22). Of line 6_3 chickens used in this study, only one chicken developed LL and only one chicken had bursal transformation at 10 wk of age, confirming the resistance of line 6_3 chickens to ALV tumors (25). Line 6_3 chickens are known to be susceptible to infection with subgroup A ALV but rarely develop tumors (25). Line 7_1 chickens are not fully defined for their susceptibility to ALV-A and ALV-B (3), but recent data indicate some breeders are susceptible to ALV-A (B. Lupiani and A. Fadly, unpubl.). These chickens were susceptible to ALV-J

infection and tumor, as indicated by bursal transformation (20%) at 10 wk of age and the development of tumors in three chickens (one chicken from the embryo-inoculated group and two chickens from the group inoculated at hatch). Viremic-tolerant chickens are more likely to die from LL than are those that develop antibody (26). The incidences of ALV-J infection and tumors in line 0 and $15I_5$ chickens were higher in embryo-inoculated chickens than in chickens inoculated at hatch; generally, in the present study, chickens inoculated with ALV-J as embryos had the highest incidence of viremia and tumors, confirming previous reports that embryonic infection with ALV results in high incidences of viremia and tumors (14,26). Also, the incidence of ALV tumors is known to be influenced by age of exposure (14).

Results from microscopic examination of bursal tissues for ALV-induced transformation suggest that ALV-J can transform bursal follicles and may account for the LL manifestation that was observed as a predominate lesion in white leghorn chickens used in the present study. Previous work (24) showed that line 0 chickens developed ML and not LL. Differences in response to ALV-J infection in line 0 chickens used in the present study and those used by Payne *et al.* (24) may be due to the strain of ALV-J because in the previous study strain HPRS-103 of ALV-J was used.

More chickens harboring EV21 were susceptible to ALV-J infection than were chickens lacking EV21, confirming an effect of endogenous viruses on ALV-induced infection (12,15,29,30). Also, the incidence of tumors in chickens lacking EV21 (2.6%) was significantly lower ($P \leq 0.01$) than that in chickens harboring EV21 (13.8%), confirming previous reports that chickens lacking EV21 developed fewer ALV tumors than did chickens harboring EV21 (15,28,29).

White leghorn chickens develop tumors after infection with ALV-J but at a lower rate than that noted in meat-type chickens (24). Genetic transmission, but not contact exposure of EV21, increased the incidence of tumors after ALV infection at hatch (15). Congenital transmission of EV21 influenced the incidence of ALV-induced tumors (29), and cellular resistance to subgroup E ALV in late-feathering dams limited congenital transmission of EV21 to the progeny (28). Whether or not EAV viral sequences in the envelope gene of ALV-J (6,7) have an influence on ALV-J–induced tumor formation is not known.

Although ALV-J has been encountered primarily in meat-type chickens, data from the present study agreed with those obtained in 1991 by Payne *et al.* (24) that under experimental conditions white leghorn chickens are susceptible to ALV-J infection and tumors. However, the primary tumors noted in the present study were LL and hemangiomas but not ML. Therefore, the tumor response noted in the present study was different from that noted in previous studies (24). This difference could be explained by strain of ALV-J because strain HPRS-103 of ALV-J was used in the previous study (24). Data from the present study show that EV21 influences ALV-J viremia and antibody production in some strains of white leghorn chickens.

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